Rationale for the Use of Combination Injectable Therapy in Patients With Type 2 Diabetes Who Have High A1C (≥9%) and/or Long Duration (>8 Years): Executive Summary

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Recommended A1C targets for people with type 2 diabetes are between 6.5 and 8%; however, real-world data suggest that an increasing proportion of people with diabetes have suboptimal control, and ~15% have an A1C level >9%. People with A1C >9% are at increased risk for micro- and macrovascular complications and require treatment intensification to improve glycemic control as early as possible.

In a series of short videos now available on the *Clinical Diabetes* website, the authors discuss the pathophysiological changes that occur during the progression of type 2 diabetes, with particular focus on the key role of declining β-cell function. The authors review clinical characteristics—long diabetes duration and A1C ≥9%—that are indicative of diminishing β-cell function, and they discuss the clinical data that support the use of available treatment options for these individuals, consistent with current diabetes treatment guidelines.

This article is intended to briefly summarize those discussions. The videos described below are available in their entirety, along with short biographies of the authors, at https://clinical.diabetesjournals.org/content/combination-injectable-therapy.

Video Summaries

Need for Glycemic Control in Individuals With A1C ≥9% (Video 1)
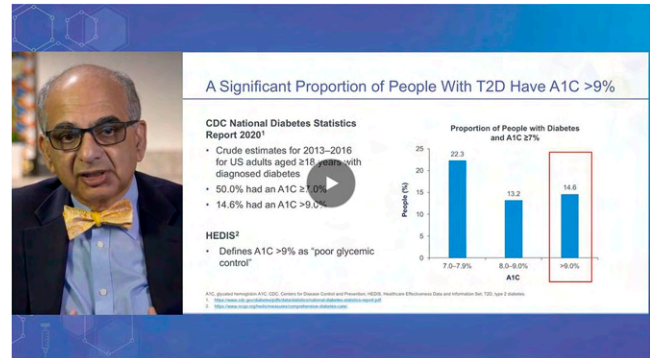
Video 1. Need for Glycemic Control in Individuals With A1C ≥9%. Available from https://bcove.video/3bda5FB.

Current treatment guidelines for people with type 2 diabetes from the American Diabetes Association, the American Association of Clinical Endocrinologists, the American College of Endocrinology, and the American College of Physicians recommend A1C targets within the range of 6.5–8% (1–3). However, public health reports suggest that a significant proportion of U.S. adults with diabetes have an A1C >9% (4), which is defined as "poor glycemic control" by the Healthcare Effectiveness Data and Information Set (5). Furthermore, A1C levels >9% can negatively affect reimbursement (e.g., through a decrease in the star ratings used to assess quality and performance) (6).

In this video, the authors discuss the deleterious health consequences for patients with high A1C levels, including data from the Diabetes & Aging Study, which demonstrated increased risk of microvascular events in individuals with A1C ≥9% (7). Data showing the relationship between the cumulative burden of microvascular disease and increased risk of cardiovascular disease (and the associated risk factors of hyperglycemia, hypertension, and dyslipidemia) in individuals with type 2 diabetes are also reviewed (8).

The UK Prospective Diabetes Study (9) showed that a 1% reduction in A1C was associated with a 37% reduction in the risk of microvascular complications. Although A1C targets differ among guidelines, all recommend individualization

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of care and include caveats that targets should be relaxed in individuals at risk for hypoglycemia or with significant comorbidities and made more stringent for others, such as those with long life expectancy.

Role and Clinical Characteristics of Beta-Cell Dysfunction in the Progression of Type 2 Diabetes (Video 2)
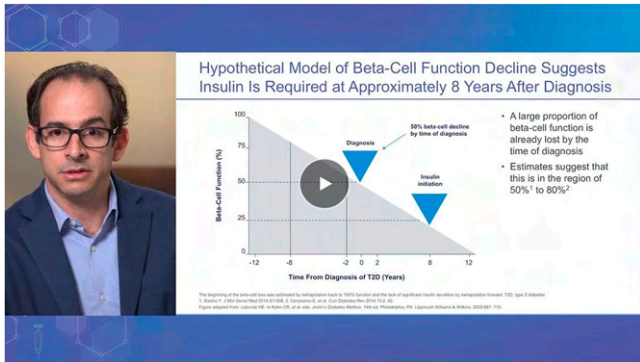
Video 2. Role and Clinical Characteristics of Beta-Cell Dysfunction in the Progression of Type 2 Diabetes. Available from https://bcove.video/306wFte.

The transition from impaired glucose tolerance to type 2 diabetes is associated with the progressive loss of β-cell mass and secretory capacity, which results in the inability to compensate for increased insulin resistance (10). In this video, the authors discuss the pathophysiological changes that occur during the progression of type 2 diabetes, with a particular focus on the key role of declining β-cell function. Estimates suggest that 50–80% of β-cell function is already lost at the time of type 2 diabetes diagnosis and that, ~8 years after diagnosis, β-cell function has declined to the point that insulin therapy may be needed (11).

The authors review clinical characteristics that are indicative of diminishing β-cell function. They discuss the results of the recent All New Diabetics in Scania cohort study (12), which suggest that nearly one-fifth of individuals with type 2 diabetes have severe insulin-deficient diabetes with characteristics such as younger age, lower BMI, and high A1C that are similar to those with type 1 diabetes; these individuals represent a higher proportion of the total type 2 diabetes population than is generally appreciated (12).

The authors review the complexities of determining whether β-cells are committed to failure and discuss the deleterious effect of glucotoxicity (i.e., high A1C) on β-cells, particularly when persistent (13). The authors also discuss the requirement for aggressive treatment in this setting to prevent not only complications, but also further deterioration of β-cell function. They advise that, ideally, clinicians should select agents

that do not act through a β-cell mechanism and do not over-stimulate β-cells. The assessment of β-cell function as measured by C-peptide is discussed, and data from the Veterans Affairs Diabetes Trial cohort, which showed that C-peptide levels decrease with increasing duration of diabetes, are reviewed (14). However, the authors agree that C-peptide testing is often not practical in the primary care setting.

Increased awareness of patient characteristics may help practitioners to identify individuals who may be at risk for β-cell failure and for whom treatments that can facilitate β-cell rest should be considered. These characteristics include long duration of type 2 diabetes (>8 years), high A1C (≥9%) (15,16), and previous use of insulin secretagogue agents (17).

Clinical Implications of Beta-Cell Status on Therapeutic Selection (Video 3)
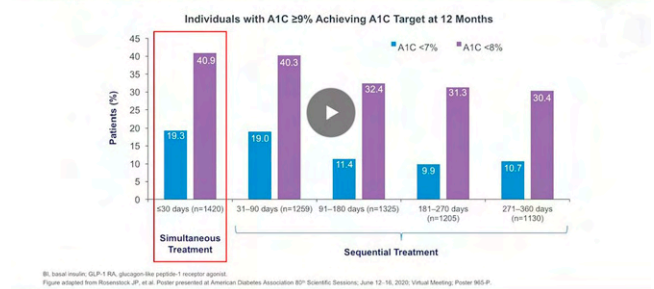
Video 3. Clinical Implications of Beta-Cell Status on Therapeutic Selection. Available from https://bcove.video/3bcEALW.

Several studies have shown that treatment with agents that stimulate β-cell function, including sulfonylureas and dipeptidyl peptidase 4 inhibitors, is associated with accelerated β-cell exhaustion and deterioration of glycemic control (18,19). In this video, the authors discuss treatments that do not stimulate β-cells.

The authors review evidence showing that early insulin therapy preserves β-cell function and can improve overall glycemic control (20). They also discuss glucagon-like peptide 1 receptor agonists (GLP-1 RAs), which are the recommended first injectable therapy for the majority of people with type 2 diabetes (1,2) because of their glycemic efficacy and lack of association with weight gain and hypoglycemia.

GLP-1 RAs suppress glucagon secretion and slow gastric emptying; however, agents within this class have differing mechanisms of action. Long-acting GLP-1 RAs act via glucose-dependent stimulation of insulin secretion and are hypothesized to increase secretory stress on β-cells; they also cause continuous stimulation of the GLP-1 receptor and consequent tachyphylaxis of the gastric emptying effect.

In contrast, short-acting GLP-1 RAs tend to exert their action primarily via a delay in gastric emptying and, because they have only intermittent receptor engagement, do not cause tachyphylaxis and are hypothesized to induce β-cell rest (21). The authors review results from a descriptive post hoc analysis, which showed that short-acting GLP-1 RA therapy reduced A1C, fasting plasma glucose, and postprandial glucose regardless of the level of β-cell function (22).

The rationale for combination therapy comprising a GLP-1 RA and basal insulin is based on the complementary effects of agents in these two drug classes. This combination has potent glucose-lowering actions and is associated with less weight gain and hypoglycemia than intensified insulin regimens (1). Real-world data have shown that, for the majority of individuals with A1C ≥9% and progression of type 2 diabetes despite oral therapy, neither a short-acting GLP-1 RA nor basal insulin was sufficient to reach glycemic targets when administered alone (23). Furthermore, the results of a retrospective cohort study of people with A1C ≥9% receiving oral antihyperglycemic agents who initiated both a GLP-1 RA and basal insulin in any order showed that those who initiated the two therapies on separate occasions were less likely to achieve glycemic control than those who initiated them on the same day or within 90 days of each other (24).

Two fixed-ratio combination (FRC) therapies comprising a basal insulin and a GLP-1 RA are currently available: iGlarLixi and IDegLira. iGlarLixi is an FRC of basal insulin glargine 100 units/mL and the short-acting GLP-1 RA lixisenatide 33 µg/mL that delivers doses from 15 to 60 units as a once-daily injection. IDegLira is an FRC of basal insulin degludec 100 units/mL and the long-acting GLP-1 RA liraglutide 3.6 mg/mL that delivers doses from 10 to 50 units, also as a once-daily injection.

Insulin/GLP-1 RA Fixed-Ratio Combination Therapy After Failure of Oral Antihyperglycemic Agents (Video 4)
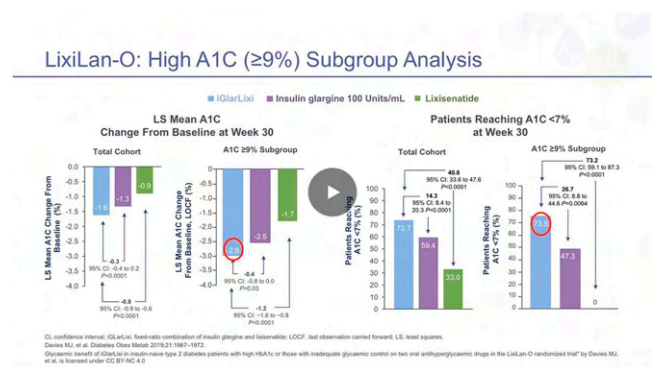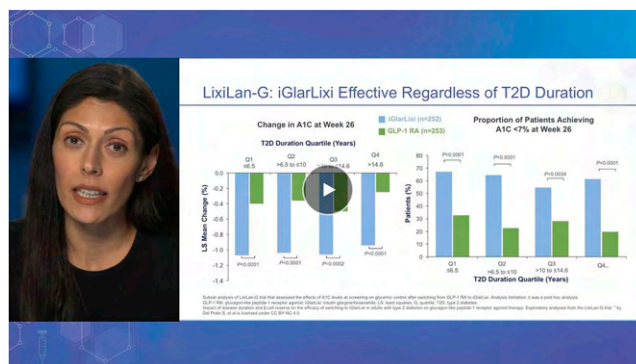

Video 4. Insulin/GLP-1 RA Fixed-Ratio Combination Therapy After Failure of Oral Antihyperglycemic Agents. Available from https://bcove.video/3sOEu3g.

In this video, the authors discuss the use of FRC therapies in individuals with type 2 diabetes and A1C inadequately controlled despite the use of oral antihyperglycemic therapy.

The efficacy and safety of the available FRC products in this patient population were investigated in open-label, randomized phase 3 studies: the LixiLan-O study for iGlarLixi (25) and the DUAL-I study for IDegLira (26). The LixiLan-O study was a 30-week, multicenter trial that compared treatment with iGlarLixi versus either insulin glargine or lixisenatide alone in adults who had received oral therapy for at least 3 months and who continued metformin therapy (25). DUAL-I was a 26-week study in adults who had received treatment with metformin with or without pioglitazone and compared daily injections of IDegLira, insulin degludec, or liraglutide (26). Reductions from baseline in A1C were greater with FRC therapies than with either of their components when used as single agents. Additionally, more people who received an FRC therapy achieved A1C targets (<7 and ≤6.5%). Mean body weight decreased with the FRC therapies, whereas it increased with basal insulin alone. Individuals who received FRC therapy reported fewer gastrointestinal adverse events than those who received a single-agent GLP-1 RA (25,26). Post hoc analyses demonstrated that the benefit of each FRC therapy over its individual components in reducing A1C is maintained in individuals with A1C ≥9% (27,28).

Insulin/GLP-1 RA Fixed-Ratio Combination Therapy After Failure of Previous GLP-1 RA Therapy (Video 5)

Video 5. Insulin/GLP-1 RA Fixed-Ratio Combination Therapy After Failure of Previous GLP-1 RA Therapy. Available from https://bcove.video/3uSzhJd.

In this video, the authors review the results of phase 3 randomized, open-label studies that assessed the efficacy and safety of FRC therapies in individuals with type 2 diabetes who had progressed despite their having received prior GLP-1 RA therapy. The 26-week LixiLan-G study enrolled adults on metformin and the maximum tolerated dose of a daily, twice-daily, or weekly GLP-1 RA, with or without pioglitazone and/or a sodium–glucose

cotransporter 2 inhibitor and compared continuation of the GLP-1 RA with switching to iGlarLixi (29). In the DUAL III study, patients on a maximum-dose GLP-1 RA therapy (liraglutide once daily or exenatide twice daily) with oral agents (metformin alone or with pioglitazone and/or sulfonylurea therapy) were randomized to IDegLira once daily or to unchanged GLP-1 RA, continuing oral agents at pre-trial doses (30).

For both studies, the mean decrease in A1C from baseline was greater for the FRC than for stand-alone GLP-1 RA therapy, as was the proportion of individuals achieving target A1C levels. Weight change and gastrointestinal adverse events appeared to be higher with FRC therapy than with a separate GLP-1 RA, but this was likely a consequence of switching from previous GLP-1 RA therapy. The results of a post hoc analysis of the LixiLan-G study according to C-peptide quartile showed that A1C reduction was significantly greater in the iGlarLixi arm than in the GLP-1 RA arm across all C-peptide quartiles, suggesting that the level of β-cell dysfunction has little, if any, impact on A1C outcomes achieved with iGlarLixi (31).

The authors also discussed the results of a propensity score–matched analysis (32) that compared outcomes from participants who received iGlarLixi in the LixiLan-L study (33) with those of participants who received basal-bolus insulin therapy in the GetGoal Duo-2 trial (34). The results of this analysis suggest that treatment intensification with iGlarLixi may be more efficacious and better tolerated than use of basal-bolus insulin (32).

Practical Tips for Using Fixed-Ratio Combination Therapies (Video 6)
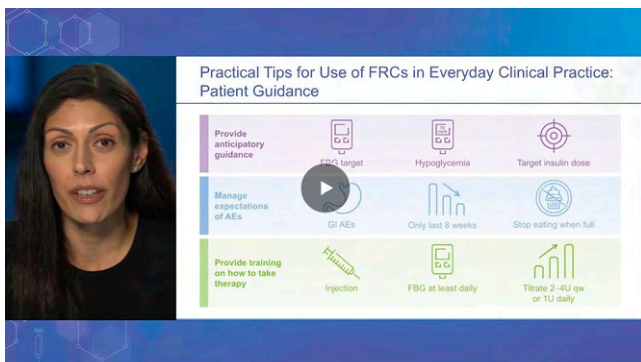
Video 6. Practical Tips for Using Fixed-Ratio Combination Therapies. Available from https://bcove.video/3qhUM2K.

The authors close their review by sharing their experience using FRC therapies, offering practical advice on patient selection, and providing points to consider before, and when initiating, an FRC therapy. Specifically, the authors focus on practical considerations for the initiation of FRCs in individuals with type 2 diabetes that is uncontrolled on two or more oral agents or on prior GLP-1 RA therapy, emphasizing that FRC therapies are particularly useful for patients with A1C ≥9% and a longer duration of type 2 diabetes. Changes to previous therapy and starting and maximum basal insulin doses are also discussed, as is the importance of anticipatory guidance on fasting plasma glucose, expectations of adverse events, and the provision of appropriate training. Finally, the authors provide practical tips for using an FRC therapy in individuals with type 2 diabetes who have renal insufficiency.

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